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(71) Applicant *(for all designated States except US)*: QUANAM MEDICAL CORPORATION [US/US]; 2255–F Martin Avenue, Santa Clara, CA 95050 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ALVARADO, Angelica [CL/US]; 750 Pomeroy Avenue, Santa Clara, CA 95051 (US). EURY, Robert [US/US]; 20487B Lockwood Drive, Cupertino, CA 95014 (US). POMERANTSEVA, Irina D. [RU/US]; 820 Bay Street, Mountain View, CA 94041 (US). FROIX, Michael [US/US]; 433 Woodstock Lane, Mountain View, CA 94040 (US).

(74) Agents: MOHR, Judy, M. et al.; Dehlinger & Associates, Post Office Box 60850, Palo Alto, CA 94306–0850 (US).

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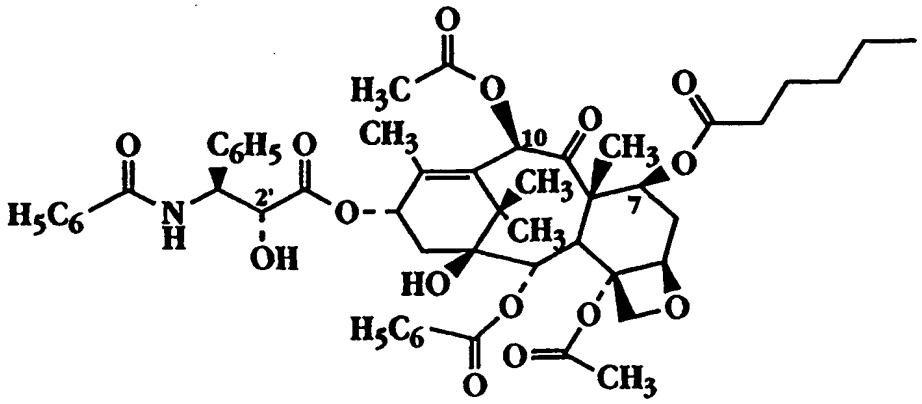

(57) Abstract

A composition for administration of a paclitaxel derivative is described. The composition includes a paclitaxel derivative having a water solubility less than that of paclitaxel and a suitable carrier. A polymer composition for administration of the poorly water–soluble paclitaxel derivative is also described. Method for treating restenosis are also described.

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form can be a polymer matrix with the therapeutic agent incorporated within. When the agent is soluble in the polymer matrix, the agent is released by diffusion through the matrix and into the surrounding environment. When the agent is not soluble in the polymer matrix, such as paclitaxel, the dosage form is prepared from a biodegradable polymer matrix, for release of the agent as the matrix degrades.

U.S. Patent No. 5,716,981 to Hunter describes another approach to formulation of the poorly water-soluble paclitaxel into a polymer carrier for *in vivo* use. The compound is combined with a carbohydrate, protein or peptide matrix, and the matrix is combined with the polymer carrier. In this way, the poorly soluble drug is coated or surrounded by a hydrophilic shell, for formulation into the polymer carrier.

In summary, the convention in the art is to design a water-soluble derivative or analogue of paclitaxel, and of other compounds, for ease of formulation and administration. The art has not recognized the value in poorly water-soluble paclitaxel derivatives for *in vivo* therapy.

Summary of the Invention

In one aspect, the invention includes a composition for administration of a paclitaxel derivative composed of a paclitaxel derivative having a water solubility less than that of paclitaxel, as measured by relative retention time on a reverse phase HPLC column, where the paclitaxel derivative is incorporated into a suitable carrier.

In one embodiment, the paclitaxel derivative is a compound derivatized at the 2', 10 or 7 position of taxol. In a preferred embodiment, the paclitaxel derivative is 7-hexanoyl taxol.

In another embodiment, the carrier is a polymer capable of solubilizing the paclitaxel derivative. Such a polymer, in one embodiment, forms a stent for placement in a target lumen, and exemplary polymers are acrylate, methacrylate and polyalkyleneoxide polymers.

In another embodiment, the carrier is a polymer and the paclitaxel derivative is incorporated into the polymer in particulate form. In still another embodiment, the carrier is a liposome and the paclitaxel derivative is entrapped therein.

In another embodiment, the carrier is an emulsion composed of the paclitaxel derivative, a hydrophobic solvent, a hydrophilic solvent and an emulsifier.

In another embodiment, the carrier is a fluid suitable for injection, the fluid

containing the paclitaxel derivative is dissolved or suspended in particulate form.

In another aspect, the invention includes a composition for treatment of restenosis which is composed of a paclitaxel derivative having a water solubility less than that of paclitaxel, as measured by relative retention time on a reverse phase HPLC column, and where the paclitaxel derivative is incorporated into a suitable carrier.

Also described herein are polymer compositions for administration of a paclitaxel derivative. One exemplary composition is composed of greater than about 40 weight percent of an acrylate monomer and between about 2-40 weight percent of a polyalkyleneoxide monomer; and a paclitaxel derivative having a water solubility less than that of paclitaxel, as measured by relative retention time on a reverse phase HPLC column. The monomers, when polymerized, form a polymer in which the paclitaxel derivative can be incorporated, as will be further described below. The polymer composition further includes, in some embodiments, between 3-30 weight percent of a methacrylate.

In another embodiment, the acrylate monomer is butyl acrylate. In still another embodiment, the polyalkyleneoxide monomer is a polyethylene oxide, such as polyethylene oxide monomethyl ether monomethacrylate or polyethyleneglycol monomethacrylate.

The polymer composition, in another embodiment, further includes between 2-15 weight percent of an organic solvent that is miscible with the monomers.

The polymer compositions described are suitable for use in fabricating into a stent for insertion into a target lumen.

In another aspect of the invention, a method of treating restenosis is described. The method includes preparing a pharmaceutical preparation composed of a paclitaxel derivative having a water solubility less than that of paclitaxel, as measured by relative retention time on a reverse phase HPLC column, and where the paclitaxel derivative is incorporated into a suitable carrier. The preparation is administered to a patient in need.

These and other objects and features of the invention will be more fully appreciated when the following detailed description of the invention is read in conjunction with the accompanying drawings.

Brief Description of the Drawings

Fig. 1A shows the structure of paclitaxel with the 2', 7 and 10 carbon positions indicated;

Fig. 1B shows the structure of a paclitaxel derivative formed by replacing the

hydroxyl group at the 7-carbon position in taxol with an ester;

Fig. 2 is an illustration of an HPLC trace showing the relative water solubilities of paclitaxel and 7-hexanoyl taxol;

Figs. 3A-3C show a support stent (Fig. 3A) suitable for carrying a polymer sleeve (Fig. 3B) or polymer members (Fig. 3C) containing a water-insoluble paclitaxel derivative or other compound;

Figs. 4A-4C illustrate another embodiment of a support stent in its small, unexpanded condition (Fig. 4A) and in its larger diameter, expanded condition (Fig. 4B) which is suitable for carrying polymer members positioned about the rigid support stent regions (Fig. 4C); and

Figs. 5A-5C illustrate yet another embodiment of a support stent in its small, unexpanded condition (Fig. 5A) and in its larger diameter, expanded condition (Fig. 5B) which is suitable for carrying polymer members about the rigid support stent regions (Fig. 5C).

Detailed Description of the Invention

I. Definitions

"Acrylate monomer" as used herein refers to a monomer capable of forming a polymer of acrylic acid or its esters with a $-(CH_2\text{-}CH(COOR))_n-$ structure. The R group is typically a group having between 1-50 carbon atoms, more preferably between 1-20 carbon atoms.

"Acrylate" or "acrylate polymer" refers to a polymer, usually a copolymer, prepared from an acrylate monomer.

"Methacrylate monomer" as used herein refers to a monomer for formation of a polymer of methacrylic acid or its esters with a $-(CH_2\text{-}C(CH_3)(COOR))_n-$ structure. The R group is typically a group having between 1-50 carbon atoms, more preferably between 1-20 carbon atoms.

"Methacrylate" or "methacrylate polymer" refers to a polymer, usually a copolymer, prepared from a methacrylate monomer.

"Polyalkyleneoxide" refers to a polymer having the general structure $R^1(OCH_2(CHR^2OCHR^3)CH_2O)_nR^4$, where the R^2 and R^3 can be H or a C1-C10 alkane, and the end groups R^1 and R^4 can be H or any suitable end moiety, such as CH3 to give a

methoxy, or various ethers. Exemplary polyalkyleneoxides include polyethylene oxide (polyethylene glycol), polyethylene oxide monomethyl ether monomethacrylate, polypropylene glycol.

"Polymer" as used herein refers to homopolymers and copolymers, including random, alternating and block copolymers.

II. Paclitaxel Derivatives

In one aspect, the invention includes a composition for administration of a paclitaxel derivative, and in particular, a derivative that has poor water solubility, as will be discussed below. Paclitaxel (Taxol®) is an anti-microtubule agent extracted from the needles and bark of the Pacific yew tree, *Taxus brevifolia*. The structure of the drug is shown in Fig. 1A, and the reference numerals 2', 7 and 10 in the figure identify some of the carbon positions on the taxane ring that are known to be suitable for derivatization or modification (see for example U.S. Patent Nos. 5,412,116; 5,629,433; 5,283,253; 5,294,637).

Fig. 1B shows the structure of one example of a paclitaxel derivative suitable for use in the present invention. As seen, the compound in Fig. 1B is modified at the 7-carbon position by replacing the hydroxyl with a hexanoyl ester.

According to an important feature of the invention, the paclitaxel derivative for use in the invention, such as the 7-hexanoyl taxol in Fig. 1B, is less water-soluble than paclitaxel (Fig. 1A). The water solubility of 7-hexanoyl taxol relative to paclitaxel was determined via HPLC analysis using a reverse phase column and illustrations of the HPLC traces are shown in Fig. 2. The column employed was made of silica with the hydrophilic Si-OH functionalities converted to hydrophobic diphenylmethyl functionalities. The mobile phase was acetonitrile/water. In this column, a hydrophilic or water soluble test material is retained primarily in the aqueous mobile phase, resulting in the water soluble compounds eluting from the column earlier than hydrophobic or water insoluble compounds. As seen in Fig. 2, paclitaxel (solid line) has a retention time of 18.5 minutes. The 7-hexanoyl taxol (dashed line) has a retention time of 30.9 minutes. The longer retention time of the 7-hexanoyl taxol, *e.g.*, the hydrophobic shift, indicates that the derivative is less water soluble than paclitaxel.

That the 7-hexanoyl taxol is less water soluble than paclitaxel is consistent with the fact that an ester is less water soluble than the individual components. For example, ethyl

acetate is an ester of ethanol and acetic acid, both of which are water soluble, but the ethyl acetate ester of the two is not water soluble. Similarly, 7-hexanoyl taxol has an hexanoyl ester at the 7-carbon position. More generally, the invention contemplates 7-position esters of any length, provided the derivative is less water soluble than paclitaxel.

Using such guidance, those of skill in the art can contemplate a variety of derivatives of paclitaxel that are likely to be less water soluble than paclitaxel. The invention contemplates use of such derivatives. Such derivatives can be readily prepared by those of skill in the art.

In studies performed in support of the invention, the *in vitro* cytotoxicity of 7-hexanoyl taxol was compared to paclitaxel. As described in Example 1, LC_{50} values, which signify the concentration of drug at which 50% of the cells are killed, were determined in five cell lines. The results are shown in Table 1.

Table 1

Cell Type/Line	7-hexanoyl taxol LC_{50} (μM)	Paclitaxel LC_{50} (μM)
colon cancer/HT 29	30	30
melanoma/M14	1.1	100
melanoma/SK-MEL-2	> 100	100
non-small cell lung cancer/NCI H226	> 100	70
ovarian cancer/OVCAR-5	50	> 100

As seen in Table 1, the 7-hexanoyl taxol was more cytotoxic to melanoma/M14 cells and to ovarian cancer/OVCAR-5 cells. 7-hexanoyl taxol and paclitaxel had equal toxicities to colon cancer/HT 29 cells. Paclitaxel was more cytotoxic to melanoma/SK-MEL-2 cells and to the non-small cell lung cancer cells.

III. Dosage Forms Containing the Insoluble Derivatives

The water-insoluble paclitaxel derivatives of the invention are contemplated for use in a variety of dosage forms for delivery and treatment of conditions characterized by an undesired proliferation of cells. In particular, atherosclerosis and restenosis are two conditions characterized by abnormal cell proliferation and, in preferred embodiments of the invention, are treated using the water-insoluble derivatives of the invention.

Atherosclerosis is a form of chronic vascular injury in which some of the normal vascular smooth muscle cells in the artery wall change and develop "cancer-like" behavior. The cells become abnormally proliferative, invading and spreading into the inner vessel lining, blocking blood flow and making the vessel susceptible to complete blockage by blood clotting.

Restenosis is the recurrence of stenosis or artery stricture after corrective surgery and has been referred to as a form of accelerated atherosclerosis. Restenosis is due to a complex series of fibroproliferative responses to vascular injury and is characterized by vascular smooth muscle proliferation, migration and neo-intimal accumulation.

In a preferred embodiment of the invention, a sustained release dosage form is used to treat restenosis. Restenosis occurs after coronary artery bypass surgery, artherectomy, laser ablation, heart transplantation and, in particular, after coronary balloon angioplasty and endovascular stenting. Generally, one-third of patients undergoing any one of these procedures will develop restenosis within 6 months. Accordingly, a therapeutic dosage form designed to release a water-insoluble paclitaxel derivative for a time period of at least 2 months, preferably for about 4 months, and more preferably for about 6 months, is contemplated.

Some exemplary therapeutic dosage forms which provide such sustained release will now be described.

A. Implantable Medical Devices

The water-insoluble paclitaxel derivatives are contemplated for use as a coating for implanted medical devices, such as tubings, shunts, catheters, artificial implants, pins, electrical implants such as pacemakers, and especially for arterial or venous stents, which will be described in detail below. In these devices, the derivative can be bound to an implantable medial device or can be passively adsorbed to the surface of the device. For example, metal devices can be coated with polymer-drug solution by dipping the device in the solution or by spraying the device with the solution.

1. Stents

In a preferred embodiment, the medical device is a radially expandable stent which carries the water-insoluble paclitaxel derivative to a target site in a vessel. Endovascular stents are well known in the art and are commercially available. Such stents are typically

made of a biocompatible metal, such as such as nickel-titanium alloys and stainless steel, or are composed of polymer, as has been described in, for example, in U.S. Patent Nos. 5,163,952 and 5,603,722.

For purposes of the present invention, a metal stent would be used as a support stent for a polymer sleeve, sheath or member which contains the water-insoluble paclitaxel derivative. A variety of polymers suitable for incorporation of a water-insoluble paclitaxel derivative and for formation of a coating layer or sleeve onto the metallic stent are known to those of skill in the art, and in particular methacrylate and acrylate polymers are suitable.

The metal support stent can take a variety of forms, and is generally suitable for implantation into a body lumen in a collapsed or small-diameter condition and for expansion to a larger diameter condition upon placement at the site to be treated. Stents known in the art and suitable for use in the present invention include pressure-expandable stents, self-expanding stents and stents which expand in response to an applied stimulus, such as heat. An exemplary pressure-expanding stent is described in United States Patent Nos. 4,776,337 and 4,733,665 to Palmaz. Pressure-expandable stents are typically radially expanded by means of a balloon angioplasty catheter, as is known in the art. Self-expanding stents, such as the stent described by Gianturco in United States Patent No. 4,580,568 and by Wallsten in United States Patent No. 4,544,771, radially expand due to the inherent spring tension of the stent. The stents expand to a larger diameter after being released from a constraining force which restricts it to a smaller diameter. Another sort of self-expanding stent includes stents made of shape-memory material, such as nitinol or shape-memory polymers described by Froix in United States Patent No. 5,163,952.

Stents prepared of polymer and loaded with the water-insoluble paclitaxel derivative are also contemplated. In particular, stents composed of acrylate and methacrylate-based polymers, such as the shape-memory polymers described by Froix in United States Patent No. 5,163,952, loaded with the drug are suitable.

In support of the present invention, studies were conducted using a metal support stent which carried one or more polymer sleeves about its outer circumference. The polymer sleeve(s) contained the water-insoluble paclitaxel derivative, 7-hexanoyl taxol. Preparation of a polymer sleeve containing 7-hexanoyl taxol is described in Example 2. The exemplary polymer sleeves were prepared from an acrylate/methyacrylate monomer mixture and polymerized using a methacrylate crosslinker. 7-hexanoyl taxol was added to the polymer by contacting the polymer with a concentrated solution of the 7-hexanoyl taxol

in a suitable organic solvent.

As will be described below, the drug-loaded, support stent carrying one or more polymer sleeves was deployed in the coronary arteries of pigs for evaluation and was compared to the same stent carrying paclitaxel.

The polymer composition described in Example 2 is also suitable for use in preparing a polymer stent capable of carrying the water-insoluble paclitaxel derivative. The polymer formulation is also suitable to apply a thin polymer coating to either a metal or polymer stent for purposes of carrying the water-insoluble paclitaxel derivative.

2. Liposomes

In another embodiment, the water-insoluble paclitaxel derivative is entrapped in a liposome for administration is contemplated. Liposomes are completely closed bilayer membranes containing an entrapped aqueous phase. Liposomes can have a single membrane bilayer (unilamellar liposomes) or can have multiple bilayers, each separated from the next by an aqueous layer (multilamellar liposomes). Liposomes can carry hydrophilic drugs entrapped in the aqueous core or in the aqueous space between lipid bilayers. Hydrophobic drugs can be entrapped within the lipid bilayer of the liposomes. The use of liposomes as *in vivo* drug carriers is well known in the art.

Liposomes for use in the present invention can be prepared using any one of several known, conventional liposome preparation techniques. For example, a phospholipid or a mixture of phospholipids along with the water-insoluble paclitaxel derivative is suspended in an organic solvent. The solvent is then evaporated leaving a drug-loaded phospholipid film. An aqueous phase is then added with stirring to the dried film to form liposomes, where the bilayer of the liposomes have the hydrophobic tails of the lipid oriented toward the center of the bilayer and the hydrophilic, polar heads oriented toward the aqueous phase. The water-insoluble paclitaxel derivative is entrapped in the hydrophobic portion of the lipid bilayer. The liposomes are then sized by extrusion or sonication to the desired size.

The liposomes so formed can be administered intravenously. To provide a more sustained release formulation, the liposomes can be incorporated into a polymer coating on a medical device or can be formulated into a gel composition for site specific placement.

3. Microparticles

Polymeric microparticles which entrap the water-insoluble paclitaxel derivative are also contemplated. The microparticles can be composed of any suitable polymer by procedures known to those in the art. The polymer can be biodegradable or non-biodegradable to provide a sustained release formulation.

4. Emulsion or Injectable Formulation

The water-insoluble derivative can also be formulated using well-known pharmaceutical formulation compositions and procedures into an emulsion suitable for *in vivo* administration. The emulsion consists of, in addition to the derivative, a hydrophobic solvent, a hydrophilic solvent and an emulsifier to stabilize the phases.

IV. *In vivo* Testing

In studies performed in support of the invention a stent carrying the water-insoluble derivative, 7-hexanoyl taxol, was prepared and inserted into the arteries of pigs. The stent was composed of a metal support stent carrying a polymer stent thereon and is depicted in Fig. 3A-3C. Fig. 3A shows the metal support stent 10 alone in an expanded, large diameter condition. The stent is composed of unit cells, such as unit cells 12, 14, 16, joined in a radial direction to form a plurality of unit cells 18. Each unit cell is expandable to move the stent from a small-diameter condition, for insertion into a body lumen, to a large-diameter condition, for deployment into the body lumen. Support stent 10 as shown is composed of four pluralities of unit cells, 18, 20, 22 and 24. The pluralities of unit cells are joined radially by a connecting segment, such as connecting segments 26a, 26b, 26c, which join pluralities 18, 20; 20, 22; and 22, 24, respectively. As can be appreciated, the stent can be composed of any number of pluralities to give any desired stent length, and the dimensions of each unit cell can readily be varied to determine stent length and diameter. The stent in regions which correspond to each plurality of unit cells, is relatively rigid compared to the regions between each plurality and corresponding to the connecting segments. This is an important feature of the stent, since the more flexible regions corresponding to the connecting segments gives better flexibility and tractability to the stent for easier navigation and placement in vessels. The stent of Fig. 3A is described in detail in co-owned PCT Publication No. WO 99/49811.

Fig. 3B shows the metal stent of Fig. 3A with a continuous polymer sheath 30 encasing the metal support stent. The outer polymer sleeve is prepared, for example, as set forth in Example 2, and contains the 7-hexanoyl taxol, or other compound. The sleeve is carried coaxially about the outer circumference of the support stent and takes the form of a flat sheet rolled into a cylindrical or tubular shape by overlapping the edges 32, 34 of the sheet. It will be appreciated that the initial configuration of the tubular member is not limited to a flat sheet, but can also be prepared from an extruded tube-form.

Fig. 3C illustrates another embodiment of a stent for use in the invention, where stent 40 is composed of metal stent 10 of Fig. 3A and includes a plurality of polymer members about the outer circumference. Stent 10 has four rigid regions which correspond to the unit cell pluralities 18, 20, 22, 24 (see Fig. 3A). By "rigid" it is meant that in this region of the stent, flexure in the radial direction is minimal, especially when compared to the radial flexure of the regions corresponding to where the connecting segments join the rigid regions. These flexible regions are identified in Fig. 3C as regions 42a, 42b, 42C. The polymer members are disposed coaxially about the outer stent surface only in the rigid stent regions, as are polymer members 44, 46, 48, 50, leaving the flexible regions 42a, 42b, 42c, exposed or uncovered. This positioning of the polymer members offers the advantage of carrying a polymer member for administration of a therapeutic compound, while maintaining the flexibility offered by the articulating stent. The configuration also overcomes problems associated with drape and sag of the polymer member when it covers the regions of flexure (as in the embodiment of Fig. 3B), as structural support for the polymer is less adequate than in the rigid regions of the support stent.

Figs. 4A-4C illustrate another exemplary support stent suitable for use in the invention. A metal support stent 60 is shown in Fig. 4A in its small-diameter, unexpanded condition. Stent 60 has two regions of rigidity, 62, 64, where flexure in the radial direction is minimally possible. The two rigid regions are joined by one or more connecting segments, such as segments 66a, 66b, and define a flexible stent region 68. The same stent is shown in Fig. 4B in its larger diameter, expanded condition, where the rigid regions 62, 64 and the flexible region 68 are clearly indicated. Stent 60 includes at least one polymer member disposed about one or more of the rigid stent regions. As shown in Fig. 4C, polymer members 70, 72 cover rigid regions 62, 64, respectively, leaving flexible

region 68 uncovered and exposed.

Another example of a support stent with polymer members is illustrated in Figs. 5A-5C. Here the support stent 80 in its small diameter condition is shown in Fig. 5A where rigid stent regions 82, 84 are joined by one or more connecting segments 86a, 86b, which define a region of flexibility 88. The stent in its large diameter, expanded condition after placement in a vessel is shown in Fig. 5B. The stent with polymer members covering the rigid stent regions is shown in Fig. 5C, where polymer members 90, 92 are positioned over rigid regions 82, 84, respectively.

The support stent is composed of a biocompatible materials, and suitable materials include metals, such as stainless steel, tungsten, titanium, gold, platinum and tantalum, alloys of these materials and others, as well as shape-memory alloys, high strength thermoplastic polymers, copolymers, including shape-memory polymers. Shape-memory copolymers including homopolymers and copolymers are contemplated.

The polymer members are composed of any biocompatible polymer, such as polyamides, polyimides, silicones and fluorinated polyolefins. A preferred fluorinated polyolefin is polytetrafluoroethylene, which can be either biaxially oriented polytetrafluoroethylene or uniaxially oriented polytetrafluoroethylene. In one embodiment of the invention, the polymer member is prepared from between 10-98 weight percent of acrylate monomer, more preferably greater than 40 weight percent, and between 2-40 weight percent of a polyalkyleneoxide monomer, more preferably between about 10-30 weight percent. An exemplary polyalkyleneoxide monomer is polyethylene oxide monomethyl ether monomethacrylate. In another embodiment, added to the acrylate monomer and the polyalkyleneoxide monomer is between 3-30 weight percent of a methacrylate monomer. Polymers formed of these monomers are described in more detail in a copending, co-owned application, which is incorporated by reference herein.

The polymer member is formed into a tubular configuration, either by fabrication or extrusion directly into a cylindrical form or by wrapping a polymer sheet into a cylindrical configuration. The polymer members are secured in an unexpanded diameter to the support stent by a mechanical means, such as by ultrasonic welding, resistive heating and laser irradiation. Alternatively, the polymer tubular member is secured to the support stent in an unexpanded diameter by a biocompatible adhesive, such as a fluorinated thermoplastic polymer adhesive. Examples of fluorinated thermoplastic include fluorinated ethylene/propylene copolymers, perfluoroalkoxy fluorocarbons,

ethylene/tetrafluoroethylene copolymers, fluoroacrylates, and fluorinated polyvinyl ethers. It is also possible that the polymer member has sufficient inherent elasticity to remain secured to the support stent in its small, unexpanded diameter and for expansion with the support stent.

The therapeutic agent can be incorporated into the polymer member by a variety of methods. For example, the polymer members can be soaked in a solution containing the agent to imbibe the drug into the polymer. The solvent can then be removed by heating or reducing pressure. The polymers members can be formed by dissolving the polymer in a solution containing the agent and allowing the solvent to evaporate to form a polymer sheet, which is then cut into sizes suitable for formation of the polymer members. Other methods are apparent to those of skill in the art.

In another embodiment of the invention, the polymer members carries two therapeutic agents, where in a preferred embodiment, the first agent is paclitaxel or a derivative of paclitaxel and the second agent is any of those recited above, preferably camptothecin, colchicine, dexamethasone, melphalan, econozole or tamoxifen.

In studies performed in support of the invention, polymer members containing 7-hexanoyl taxol were prepared from an acrylate/methyacrylate monomer mixture and polymerized using a methacrylate crosslinker, as described in Example 2. 7-hexanoyl taxol was incorporated into the polymer by contacting the polymer with a concentrated solution of the 7-hexanoyl taxol in a suitable organic solvent. Such polymer members, and polymer members similarly formed but with paclitaxel rather than 7-hexanoyl taxol, were used in combination with a support stent, as illustrated in Fig. 3C. The test and control stents were placed in the coronary arteries of pigs, as described in Example 3, and were left *in vivo* for 28 days. A metal stent not carrying a polymer member was also placed into an artery. At the time of insertion of the test and control stents, the coronary artery was characterized using a computer-based coronary angiography analysis system (Umans, V.A., *et al., JACC* 21(6):1382-1390, (1993)). Boundaries of a selected coronary artery segment were detected automatically from optically magnified and video-digitized regions of interest. The catheter used for insertion of the stents was used as a scaling device to determine the dimensions of the artery at the site of implantation. The original vessel diameter at the time of implantation was determined.

After the 28 day test period, the arteries were then explanted from the pig and pressure fixed for morphometric analysis. The minimal lumen diameter of the vessel after

the treatment period was found by determining the smallest lumen diameter in the region of stent placement. The percent stenosis was taken as one minus the stented vessel's minimum lumen diameter divided by the diameter of an unstented reference vessel time one-hundred. The percent intimal growth was also determined from the following equation: 1-[(stented vessel's minimum lumenal diameter)/(diameter of stented portion prior to stent placement)]*100. The balloon to artery ratio was also determined as a measure of the degree of distension of the vessel by the balloon. The results are shown in Table 2.

Table 2

Stent Configuration	Stent Location	Balloon to Artery Ratio	% Diameter Stenosis	% Intimal Growth
metal support/polymer segments with 7-hexanoyl taxol	right coronary artery	1.04	4	-7.1
metal support /polymer segments with 7-hexanoyl taxol	left circumflex artery	0.98	16	2.3
metal support /polymer segments with paclitaxel	right coronary artery	1.16	34	29.5
metal support stent (no drug)	left anterior descending artery	1.16	22	73.2
metal support stent (no drug)	right coronary artery	1.11	27	73.2

As can be seen from the data in Table 2, arteries treated with stents containing 7-hexanoyl taxol had the lowest percent stenosis. Compared to the stent containing paclitaxel, the stent with 7-hexanoyl taxol resulted in about a two-fold reduction in percent stenosis, for one case, and in the other case, about an 8-fold reduction in percent stenosis. The percentage intimal growth was also significantly better for the stents carrying 7-hexanoyl taxol, when compared to the stent carrying paclitaxel and to the control metal stents.

The finding that *in vivo* 7-hexanoyl paclitaxel is significantly more effective in treating restenosis than paclitaxel was surprising in view of the *in vitro* cytotoxicity results discussed above in Table 1. In those tests, in some cell lines the 7-hexanoyl taxol was more effective, however in other cell lines the paclitaxel was more effective. Based on this, the considerable improvement achieved with the 7-hexanoyl taxol *in vivo* is unexpected.

In another study in support of the invention, stents were prepared as described in Examples 2 and 3. The polymer members carried either 7-hexanoyl taxol, paclitaxel or 7-xylosyltaxol. 7-xylosyltaxol is a sugar derivative of paclitaxel and has been described in WO 96/11683. The 7-xylosyl taxol, having the hydrophilic sugar moiety, is more water-soluble than paclitaxel. The stents were placed in coronary arteries of pigs, according to the procedure described above. After the test period, the percent diameter stenosis and neointimal thickness of the arteries were determined. The percentage of diameter stenosis was determined by two procedures, via quantative coronary angiography (QCA) and via morphometric evaluation of the vessels. The later procedure is described in Example 3. The former procedure, QCA, was performed according to the procedure of Umans, *et al.* described above, with lumen dimensions determined prior to explanting the vessels for morphometric analysis. The results are reported in Table 3.

Table 3

Stent Configuration	% Diameter Stenosis (determined by QCA)	% Diameter Stenosis (determined morphometrically)	Neointimal thickness (mm)
metal support/polymer segments with 7-hexanoyl taxol	10%	9%	0.24
metal support /polymer segments with paclitaxel	20%	13%	0.28
metal support /polymer segments with 7-xylosyl taxol	63%	-	-
metal support stent (no drug)	29%	12.2%	0.33

The data in Table 3 shows that the water-insoluble paclitaxel derivative resulted in considerably lower percent diameter stenosis than the water-soluble derivative, 7-xylosyltaxol. The study also supports the data in Table 2, indicating that the water-insoluble derivative achieved lower percent stenosis and less intimal thickening than paclitaxel.

In yet another study performed in support of the invention, metal support stents carrying a plurality of polymer sleeves as depicted in Fig. 3C were prepared and tested in humans at risk for restenosis. Polymer sleeves prepared as described in Example 2 were loaded with 800 μg of 7-hexanoyl taxol. Metal stents, as depicted in Fig. 3A and as described in detail in co-owned PCT Publication No. WO 99/49811, were used as the support structure for the drug-loaded polymer sleeves. The stent sizes were between 13-17

mm in length and from 3.0-3.5 mm in diameter (after expansion) depending on the lesion and the vessel size. Stents of 13 mm in length carried 4 polymer sleeves, each loaded with 800 μg of 7-hexanoyl taxol. The stents of 17 mm in length carried 5 polymer sleeves, each loaded with 800 μg of 7-hexanoyl taxol.

Thirty-one patients at risk for restenosis and having vessel lesions were randomized into two treatment groups of 16 individuals to receive the stent carrying the drug-loaded polymer and 15 individuals to receive a metal support stent with no polymer sleeve or drug. Of the 31 patients, 46% had type A lesions, 54% had type B2 and C lesions, using the American College of Cardiology/American Heart Association (ACC/AHA) classification of lesion morphology (Kastrati, A., *et al. Circulation* 100(12):1285, (1999)).

The test and control stents were inserted into the patients via balloon catheter, and all stents were successfully placed in the selected vessel of each patient, as determined by intravascular ultrasound (IVUS; Erbel, R. *et al. Coron. Artery Dis.* 10(7):489, (1999)). For 3-8 months following stent insertion, each patient was monitored clinically, angiographically and by intravascular ultrasound (IVUS). Quantative coronary angiography (described above) and quantative coronary ultrasound were performed by an independent lab in 25 of the patients to verify the findings.

Table 4 summarizes the data from the human trial. The average minimum lumen diameter (MLD) in mm before insertion of the test stent and the minimum lumen diameter in mm after insertion and expansion of the stent for the two test groups are shown, as is the average minimum lumen diameter in mm at the follow-up visit (between 3-8 months). The percent diameter stenosis taken as the [MLD(post insertion) – MLD(follow-up)]/MLD(post insertion) was determined.

Table 4

Test Group	MLD pre stent[1] (mm)	MLD post stent[2] (mm)	MLD at follow-up[3] (mm)	% diameter stenosis[4]	months
control, metal stent (n=12)	1.2 ± 0.7	2.9 ± 0.4	0.9 ± 0.9	64.8 ± 34.3	4.0 ± 1.5
stent with polymer sleeve + 7-hexanoly taxol (n=13)	1.4 ± 0.4	2.8 ± 0.5	2.2 ± 0.4	14.2 ± 22.1	4.0 ± 0.2
p	ns	ns	0.003	0.004	ns

[1]minimum lumen diameter determined prior to stent depolyment
[2]minimum lumen diameter determined immediately after stent depolyment
[3]minimum lumen diameter determined at follow-up visit from 4-8 months after stent insertion
[4]diamter stenosis taken as [MLD(post insertion) – MLD(follow-up)]/MLD(post insertion)

As seen in Table 4, the patient test populations prior to stent insertion had similar averaged minimum lumen diameters of 1.2 ± 0.7 mm and 1.4 ± 0.4 mm in vessels normally of between 3-3.5 mm diameter. After stent deployment, the vessels in the patients of each test group were similarly expanded, to 2.9 ± 0.4 mm for the control test group and 2.8 ± 0.5 mm for the group receiving the stent in accord with the invention. At the follow-up visit for each patient the minimum lumen diameter was again determined (by IVUS and/or angiographically) and the averaged values for each test group are shown in Table 4. The group receiving a metal stent with no water insoluble paclitaxel derivative had an average minimum lumen diameter of 0.9 ± 0.9 mm, whereas the patients treated with the drug-loaded stent of the invention had a minimum lumen diameter of 2.2 ± 0.4 mm. The patients treated with the drug-loaded stent showed nearly total absence of intimal proliferation at the lesion site, including the end regions of the lesion. In contrast, the patients in the control group had significant restenosis.

In this study, the stents contained either 3.2 mg of 7-hexanoyl taxol or 4.0 mg 7-hexanoyl taxol, depending on the length of the stent. This amount of drug is administered locally to the treatment site over a period of at least 2 months, more preferably over 3 months, and most preferably over a 6 month period. The unique combination of a high drug loading achievable with selected polymers and the insoluble nature of the paclitaxel derivative provide a means to ensure sufficient drug over the time frame needed (at least 2-6 months or 3-6 months).

Table 5 compares the dose of 7-hexanoyl-taxol needed for treatment and/or prevention of restenosis when administered from a stent loaded with 4 mg of 7-hexanoyl taxol with the dosage of paclitaxel and docetaxel used in chemotherapy. For purposes of comparison it was assumed that the 4 mg stent dose is released as a bolus.

Table 5

Compound	Dosing Frequency	Duration	Dose mg/m^2	Dose $\mu g/kg$
paclitaxel (TAXOL)	every 3 weeks	i.v. over 3 hours	135-175	3375-4375
docetaxel (TAXOTERE)	every 3 weeks	i.v. over 1 hour	60-100	1500-2500
7-hexanoyl taxol from stent	single dose in stent	3-6 month release from stent	2.7*	67*
7-hexanoyl taxol from stent	single dose in stent	3-6 month release from stent	5.3*	133*

*Stent dose is calculated for a 60 kg person, 170 cm tall (body surface area 1.7 m^2). A factor of 40 is used to convert dose from mg/kg to mg/m^2.

Table 5 shows that the dose of the water-insoluble taxol derivative is significantly less than that used in chemotherapy. Accordingly, in one embodiment of the invention, the dose of the water-insoluble taxol derivative used for treatment/prevention of restenosis is 10-fold, preferably 25-fold, more preferably 50-fold less, still more preferably 100-fold lower than that used for chemotherapy. The daily dose of 7-hexanoyl taxol estimated for treatment of restenosis is 0.02-0.03 mg/m^2 using a stent designed to deliver 2.7 mg/m^2 for 3-6 months.

From the foregoing, it will be appreciated how various features of the invention are met. The composition of the invention, composed of a water-insoluble paclitaxel derivative, is incorporated into a suitable carrier for administration to a target lumen. In one preferred embodiment, the derivative is incorporated into a stent which is placed in a lumen for prevention of restenosis following angioplasty. Suitable dosages of water-insoluble derivatives can be discerned by those of skill in the art using guidance from the effective dosages of paclitaxel and similar compounds.

V. Examples

The following examples further illustrate the features of the invention and in no way are to be considered as limiting to the scope and spirit of the invention.

Example 1
In vitro Cytotoxicity

A suspension of each cell line which was diluted according to the particular cell type and the expected target cell density (5,000-40,000 cells per well based on cell growth characteristics) was added by pipet (100 μL) into a 96-well microtiter plate. The cells were allowed a pre-incubation period of 24 hours at 37°C for stabilization. At the end of the pre-incubation period (T_0), dilutions of 7-hexanoyl taxol or paclitaxel were added in 100 μL aliquots to the microtiter plate wells. The cells were incubated in the presence of the drug for 48 hours under a 5% CO2 atmosphere at 100% humidity. The cells were assayed using the sulforhodamine B assay. A plate reader was used to read the optical densities.

The LC_{50} values were taken as the concentration of compound where 100 x $(T-T_0)/T_0$ = -50. The results are shown in Table 1.

Example 2
Polymer Sleeve Preparation

The following mixture of monomers was weighed into a suitable container: 60.1% butyl acrylate (Aldrich Chemical, St. Paul MN); 30% polyethylene oxide monomethyl ether monomethacrylate (MW 1000 daltons)(NOF Corp., Tokyo Japan); and 9.8% methylmethacrylate (Aldrich Chemical). 0.05% of hexane diol dimethacrylate (Aldrich Chemical), a cross-linker, and 0.10% of Darocur® 1173 (E. Merck, Dramstadt, Germany), a photoinitiator, were added to initiate polymerization. The monomers are mixed together, purged with nitrogen and then polymerized between glass plates to form thin films having a thickness of approximately 0.14 mm. The copolymer film is cut into the desired size for formation of the sleeve.

A solution of 7-hexanoyl taxol in dimethylformamide was prepared, with the 7-hexanoyl taxol just below the solubility limit in the solvent at room temperature. A known quantity of the solution was placed on the polymer sleeve using a micropipet and allowed to absorb into the copolymer.

Example 3
In vivo Testing of Polymer Stent Containing 7-Hexanoyl Taxol

A polymer sleeve, prepared as described in Example 2, was placed about a metal, corrugated stent. The polymer sleeve contained 1500 μg of 7-hexanoyl taxol. As a comparative control, a similar stent was prepared to contain 1500 μg of paclitaxel.

The two-drug loaded stents and two control metal stents with no polymer sleeve were placed into the coronary arteries of healthy Domestic Farm Swine pigs (Pork Power, Inc.) by conventional techniques using a commercially available catheter (Advanced Cardiovascular Systems). The stents were imaged during and after the insertion procedure to ensure proper placement using conventional angiographic imaging techniques. The metal control stents were placed in two different pigs, in one pig the stent was positioned in the left anterior descending artery and in the other pig in the right coronary artery. The comparative control stent containing paclitaxel was placed in one animal in the right coronary artery. The test stents containing 7-hexanoyl taxol were placed in two pigs, one stent in the right coronary artery and the other stent in the other pig in the left circumflex artery.

Twenty-eight days after placement, the pigs were euthanized and the heart and coronary arteries explanted. The arteries were pressure fixed for morphometric analysis to determine the percent diameter stenosis and percent intimal growth. The percent diameter stenosis was taken as 1-[(stented vessel's minimum lumenal diameter)/(diameter of unstented reference vessel)]*100. The percent intimal growth was taken as 1-[(stented vessel's minimum lumenal diameter)/(diameter of stented portion prior to stent placement)]*100. The balloon to artery ratio was also determined as a measure of the degree of distension of the vessel by the balloon. The results are shown in Table 2.

Although the invention has been described with respect to particular embodiments, it will be apparent to those skilled in the art that various changes and modifications can be made without departing from the invention.

IT IS CLAIMED:

1. A composition for administration of a paclitaxel derivative, comprising

a paclitaxel derivative having a water solubility less than that of paclitaxel, as measured by relative retention time on a reverse phase HPLC column, said paclitaxel derivative incorporated into a suitable carrier.

2. The composition according to claim 1, wherein the paclitaxel derivative is a compound derivatized at the 2', 10 or 7 position of taxol.

3. The composition according to claim 2, wherein the paclitaxel derivative is 7-hexanoyl taxol.

4. The composition according to any of claims 1-3, wherein the carrier is a polymer capable of solubilizing the paclitaxel derivative.

5. The composition according to claim 4, wherein the polymer forms a stent for placement in a target lumen.

6. The composition according to claim 4, wherein the polymer includes an acrylate or methacrylate polymer or a polyalkyleneoxide.

7. The composition according to any of claims 1-3, wherein the carrier is a polymer and the paclitaxel derivative is incorporated into the polymer in particulate form.

8. The composition according to any of claims 1-3, wherein the carrier is a liposome and the paclitaxel derivative is entrapped therein.

9. The composition according to any of claims 1-3, wherein the carrier is an emulsion composed of the paclitaxel derivative, a hydrophobic solvent, a hydrophilic solvent and an emulsifier.

10. The composition according to any of claims 1-3, wherein the carrier is a fluid

suitable for injection, the fluid containing the paclitaxel derivative in dissolved or suspended particulate form.

11. Use of the composition according to any of claims 1-10 for treatment of restenosis.

12. A composition according to any one of claims 1-3, wherein said carrier is a polymer comprised of greater than about 40 weight percent of an acrylate monomer and between about 3-30 weight percent of a polyalkyleneoxide monomer, said monomers, when polymerized, forming a copolymer having the paclitaxel derivative incorporated therein.

13. The composition according to claim 12, wherein the polymer composition further includes between 3-30 weight percent of a methacrylate monomer which is copolymerized with the acrylate monomer and the polyalkyleneoxide monomer.

14. The composition according to claim 12, wherein the acrylate monomer is butyl acrylate.

15. The composition according to any one of claims 12-14, wherein the polyalkyleneoxide monomer is polyethylene oxide monomethyl ether monomethacrylate.

16. The composition according to any one of claims 12-15, wherein the polymer is fabricated into a stent.

17. A composition for use in the prevention or treatment restenosis, comprising a paclitaxel derivative having a water solubility less than that of paclitaxel, as measured by relative retention time on a reverse phase HPLC column, and said paclitaxel derivative incorporated into a suitable carrier.

18. Use of a composition comprised of a paclitaxel derivative having a water solubility less than that of paclitaxel, as measured by relative retention time on a reverse phase HPLC column, and said paclitaxel derivative incorporated into a suitable carrier in the manufacture of a medicament for the treatment or prevention or restenosis.

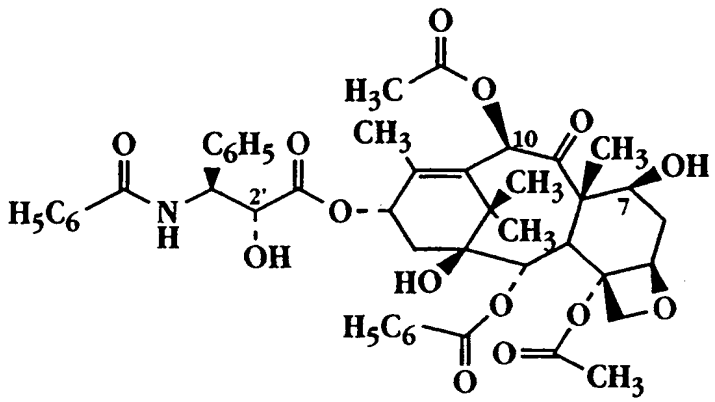

Fig. 1A

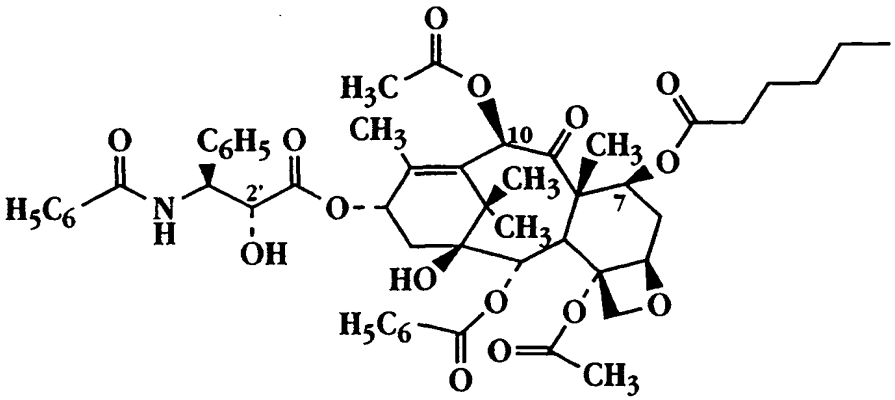

Fig. 1B

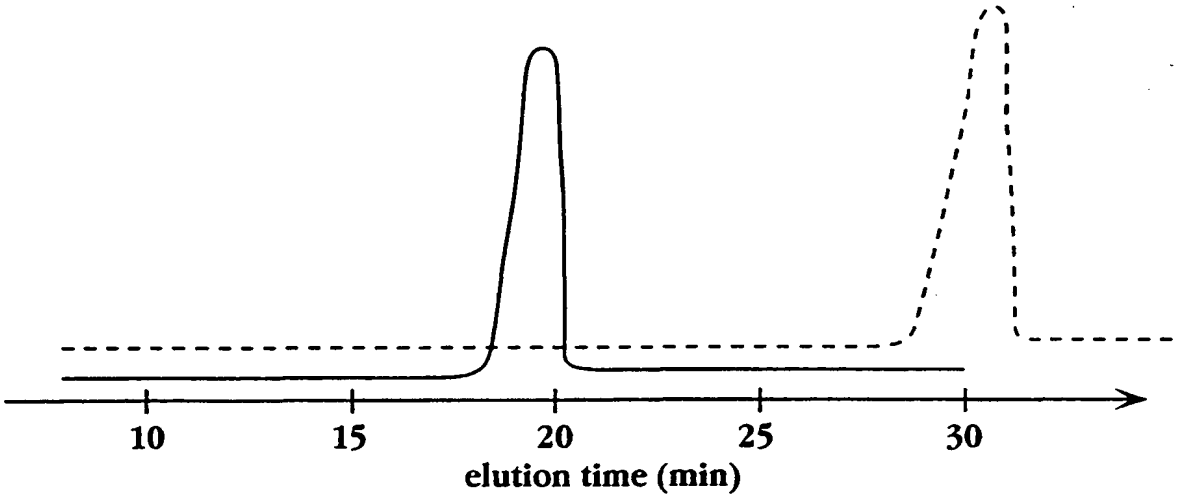

Fig. 2

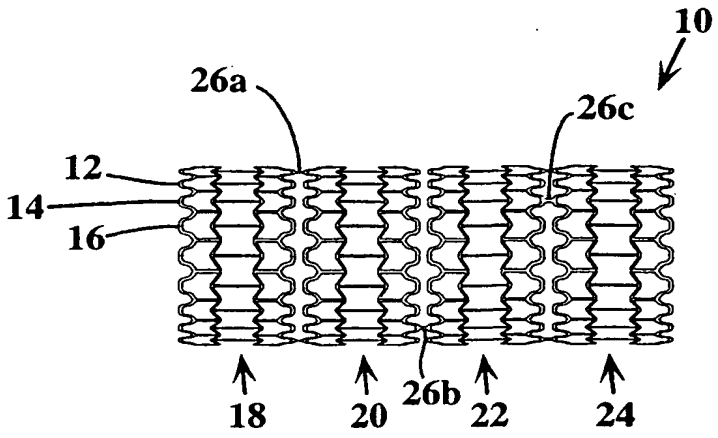

Fig. 3A

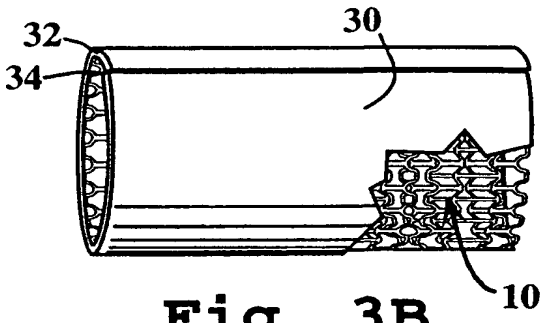

Fig. 3B

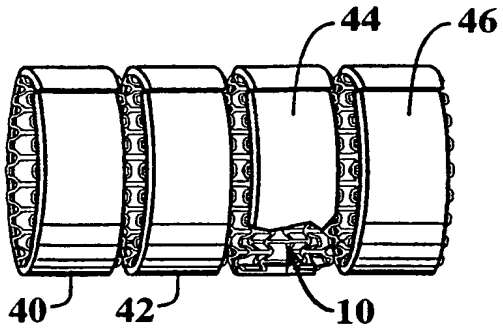

Fig. 3C

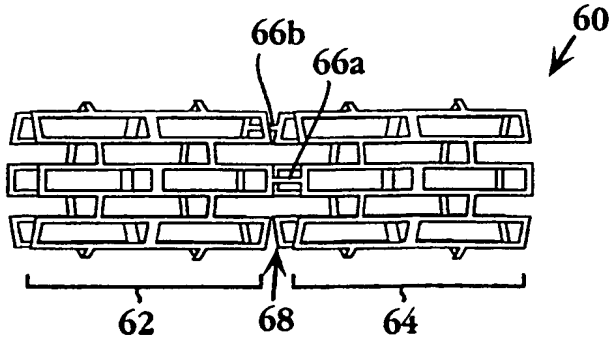

Fig. 4A

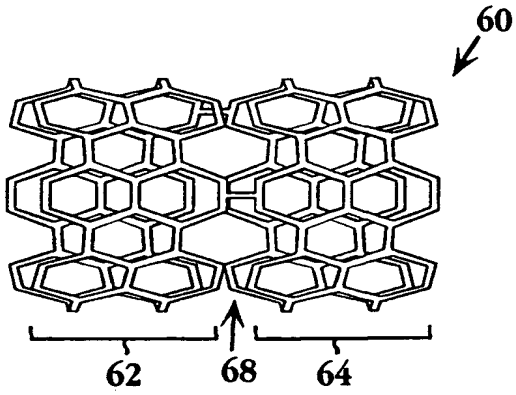

Fig. 4B

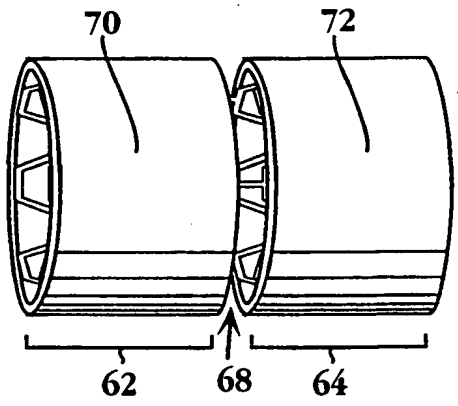

Fig. 4C

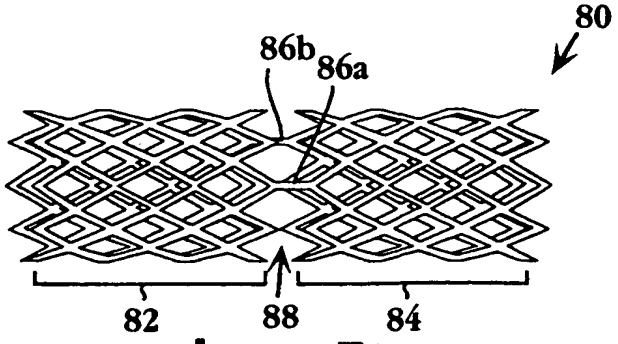

Fig. 5A

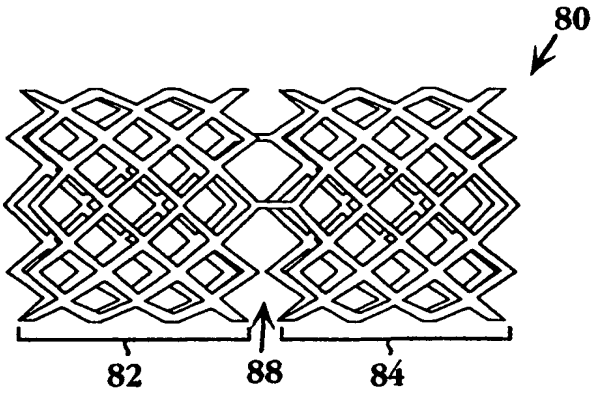

Fig. 5B

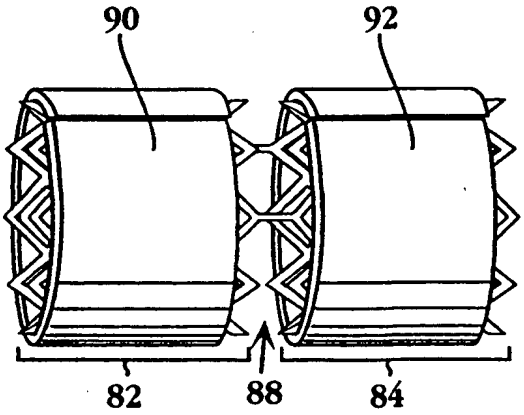

Fig. 5C

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(71) Applicant *(for all designated States except US)*: **QUANAM MEDICAL CORPORATION** [US/US]; 2255-F Martin Avenue, Santa Clara, CA 95050 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ALVARADO, Angelica** [CL/US]; 750 Pomeroy Avenue, Santa Clara, CA 95051 (US). **EURY, Robert** [US/US]; 10387B Lockwood Drive, Cupertino, CA 95014 (US). **POMERANTSEVA, Irina D.** [RU/US]; 8 Pheasantwood Terrace, Wakefield, MA 01880 (US). **FROIX, Michael** [US/US]; 433 Woodstock Lane, Mountain View, CA 94040 (US).

(74) Agents: **MOHR, Judy, M.** et al.; Dehlinger & Associates, Post Office Box 60850, Palo Alto, CA 94306-0850 (US).

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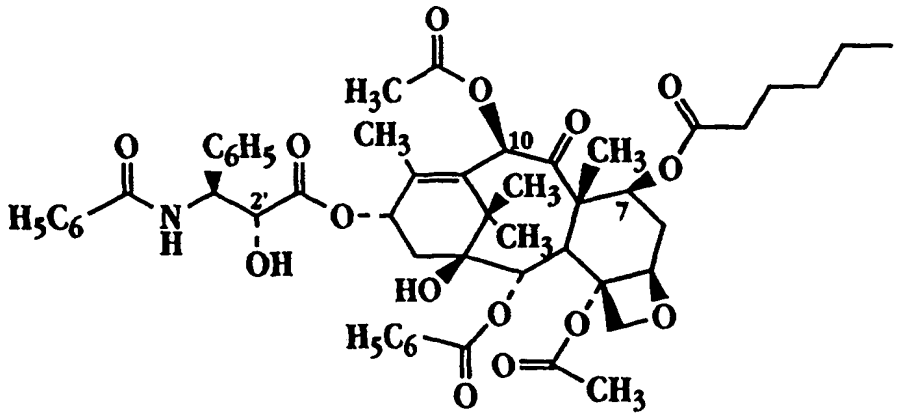
(54) Title: COMPOSITION AND METHODS FOR ADMINISTRATION OF WATER-INSOLUBLE PACLITAXEL DERIVATIVES



(57) Abstract: A composition for administration of a paclitaxel derivative is described. The composition includes a paclitaxel derivative having a water solubility less than that of paclitaxel and a suitable carrier. A polymer composition for administration of the poorly water-soluble paclitaxel derivative is also described. Method for treating restenosis are also described.

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INTERNATIONAL SEARCH REPORT

Inte ..ional Application No
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 10234 A (THE LIPOSOME COMPANY INC.,U.S.A.) 20 March 1997 (1997-03-20) claims table 1 ---	1-3,8
A	WO 97 45105 A (ANGIOTECH) 4 December 1997 (1997-12-04) claims page 18, line 3 -page 19, line 18 ---	1-18
A	WO 95 03795 A (THE SECRETARY,DPT. OF HEALTH AND UMAN SERVICES,U.S.A. GOVERNEMENT) 9 February 1995 (1995-02-09) cited in the application claims -----	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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